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RESEARCH ARTICLE

DEVELOPMENT AND IN VITRO EVALUATION OF BUCCOADHESIVE BILAYER TABLETS OF THIOCOLCHICOSIDE

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ABSTRACT

The main objective is to formulate the buccoadhesive bilayer tablets of thiocolchicoside which acts muscle relaxant with anti-inflammatory and analgesic effects.The tablets were prepared using bioadhesive polymers like Carbopol 934p, HPMC by direct compression method. Magnesium stearate were added to act as lubricant and ethyl cellulose used as impermeable backing layer which gives unidirectional buccal drug delivery. Buccal devices were evaluated for different parameters such as weight uniformity, content uniformity, hardness, surface pH, swelling index, mucoadhesive time and in vitro drug release. The results of study revealed that the formulation containing a combination of polymers like Carbopol 934p and HPMC K4M shows suitatble in vitro drug release. Invitro dissolution studies of the optimized formulation shows that the present drug release was 97.19% for 16 hrs for F3 formulation. Bioadhesive time, physicochemical properties, surface pH, swelling index were developed to a satisfactory level in terms of drug release.

Keywords: Buccal Bilayer Tablets, Thiocolchicoside, Carbopol 934p, HPMC.

INTRODUCTION

The drugs that are administered orally, solid oral dosage form represent the preferred class of products. The reasons for this preference are as follows. Tablet is unit dosage form in which one usual dose of the drug has been accurately placed by compression. Liquid oral dosage forms, such as syrups, suspensions, emulsions, solutions and elixirs are usually designed to contain one dose of medication in 5 to 30 ml and the patient is then asked to measure his or her own medication using teaspoons, tablespoon or other measuring device. Such dosage measurements are typically in error by a factor ranging from 20 to 50% when the drug is self administered by the patient.

Buccoadhesion, or the attachment of a natural or synthetic polymer to a biological substrate, is a practical method of drug immobilization or localization and an important new aspect of controlled drug delivery. The unique environment of the oral (buccal) cavity offers its potential as a site for drug delivery. Because of the rich blood supply and direct access to systemic circulation. The Buccal route is suitable for drugs, which are susceptible to acid hydrolysis in the stomach or which are extensively metabolized in the liver (first pass effect)[1].

Administration of a drug via the buccal mucosa (the lining of the cheek) to the systemic circulation is defined as buccal delivery. Despite, the buccal mucosa is significantly less permeable than the sublingual mucosa and usually not able to provide rapid drug absorption or good bioavailability; it is relatively more permeable than the skin and also offers other advantage over alternative delivery routes. The fact that the buccal mucosa is less permeable than sublingual floor makes it more desirable site for sustained drug delivery. Apart from avoiding enzymatic degradation and first pass metabolism, the non acidic conditions and lipophilic nature of the buccal tissue provide potential and promises for successful delivery of peptide and proteins.

Buccoadhesive also increases the intimacy and duration of contact between a drug-containing polymer and a buccal mucosa. The combined effects of the direct drug prolonged residence time allow for an increased bioavailability of the drug with smaller dosage and less frequent administration. Drugs that are absorbed through the buccal mucosal lining of the tissues can enter directly into the blood stream and prevent from enzymatic degradation in the GIT and avoids the first pass metabolism in the liver [2].

DRUG PROFILE

Thiocolchicoside is a muscle relaxant with anti-inflammatory and analgesic effects. It acts as a competitive GABA-A receptor antagonist and also inhibits glycine receptors with similar potency. It has powerful consultant activity. Thiocolchicoside binds to GABA-A and strychnine sensitive glycine receptors Thiocolchicoside is having some of the side effects like somnalescence, weight gain, bone pain and the common side effects may include nausea, dizziness, stomach pain and diarrhea [3,4].

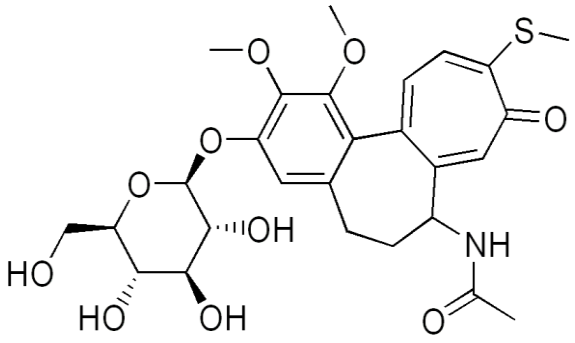

Figure 1: Thiocolchicoside: Structure

Category	:	It is muscle relax1ant with anti-inflammatory and analgesic effects.
Molecular weight		563.62 gm/mol
Half life	:	5-6 hours
Oral bioavailability	:	25%
Water solubility	:	Soluble in Water & Alcohol
Dose	:	16mg/day in divided dose 4mg four times a day or 8mg

MATERIALS AND METHODS

Table 1: Materials used for the formulation development.

1	Thiocolchicoside	VKT Pharma Pvt Ltd., Visakhapatnam	USP Grade
2	HPMC K4 M	Colorcon Asia Pvt. Ltd.,Goa	Pharmaceutical grade
3	HPMC K15 M	Colorcon Asia Pvt. Ltd.,Goa	Pharmaceutical grade
4	Carbopol 934p	Loba Chemie Pvt. Ltd., Mumbai	Pharmaceutical grade
5	PVP K 30	E.Merk (India) Ltd., Mumbai	Pharmaceutical grade
6	Magnesium stearate	Yarrow-Chem. Products, Dombivli	Pharmaceutical grade
7	Ethyl cellulose	SD Fine Chemicals Ltd.,Mumbai	Pharmaceutical grade

Preparation of Buccoadhesive bilayered Tablets [5,6] :

The buccoadhesive bilayered tablets were prepared using different polymers either alone or in combinations with varying ratios as summarized in [Table - 2]. Tablets were prepared by direct compression procedure involving two consecutive steps. The buccoadhesive drug/polymer mixture was prepared by homogeneously mixing the drug and polymers in a glass mortar for 15 min. Magnesium stearate (MS) was added as a lubricant in the blended material and mixed. The blended powder was then lightly compressed on 8 mm punch using single station tablet compression machine (Cadmach). The upper punch was then removed and backing layer material ethyl cellulose was added over it and finally compressed at a constant compression force.

Table 2: Composition of Tablets

Form.Code	Drug	Carbopol	HPMC K4M	HPMC K15M	PVP K 30	Mg Stearate	Ethyl cellulose
F1	12 mg	20 mg	38 mg	-------	5 mg	5 mg	20 mg
F2	12 mg	38 mg	20 mg	-------	5 mg	5 mg	20 mg
F3	12 mg	29 mg	29 mg	-------	5 mg	5 mg	20 mg
F4	12 mg	20 mg	-------	38 mg	5 mg	5 mg	20 mg
F5	12 mg	38 mg	-------	20 mg	5 mg	5 mg	20 mg
F6	12 mg	29 mg	-------	29 mg	5 mg	5 mg	20 mg
F7	12 mg	-------	29 mg	29 mg	5 mg	5 mg	20 mg
F8	12 mg	-------	20 mg	38 mg	5 mg	5 mg	20 mg
F9	12 mg	-------	38 mg	20 mg	5 mg	5 mg	20 mg

Construction of Calibration curve of

Calibration curves of Thiocolchicoside in phosphate buffer (pH 6.8) solutions were obtained at λmax 353 nm with a UV-VIS spectrometer (UV-1601PC, Shimadzu Corporation, Tokyo, Japan). Beer's law obeyed to construct the calibration curve was in the concentration range of 0-20 µg/ml.

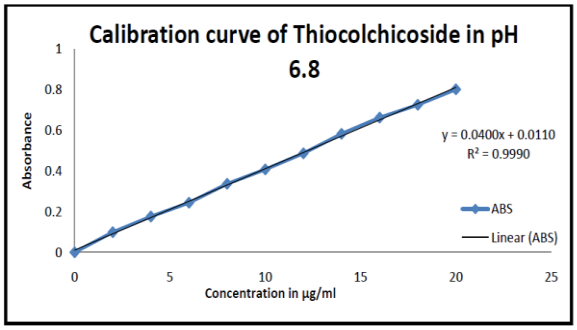

Figure 2: Calibration curve of Thiocolchiside

Evaluation of Tablets [7]

The formulated tablets were evaluated for the following physicochemical parameters

Weight Variation

Formulated tablets were tested for weight uniformity, 20 tablets were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it is within permissible limits or not. The results listed in the table 3.

Hardness

Hardness of the tablet was determined using the Pharma test; Tablet Tester. 10 tablets were tested and results are listed in the table 3.

Friability

The Electro lab friability test apparatus was used to determine the friability of the tablets. Twenty pre-weighed tablets were placed in the apparatus, which was given 100 revolutions. After which the tablets were reweighed. The percentage friability was calculated. The results listed in the table 3.

Drug Content

Five tablets of each formulation were weighed and powdered. The quantity of powder was equivalent to 12 mg. The equivalent weight was transferred into 100 ml volumetric flask and by using phosphate buffer (pH 6.8) and samples were analyzed spectrophotometrically. The results listed in table 3.

Surface pH of the buccoadhesive bilayer tablets [8]

The surface pH of the buccal tablets was determined in order to investigate the possibility of any side effects in vivo. As an acidic or alkaline pH may cause irritation to the buccal mucosa, it was determined to keep the surface pH as close to neutral as possible. The method adopted by Bottenberg et al was used to determine the surface pH of the tablet. A combined glass electrode was used for this purpose. The tablet was allowed to swell by keeping it in contact with 1 ml of distilled water (pH 6.5 ± 0.05) for 2 hours at room temperature. The pH was measured by bringing the electrode in contact with the surface of the tablet and allowing it to equilibrate for 1 minute. The results listed in table 3.

In vitro swelling studies of buccoadhesive bilayer tablets[9]

Buccal tablets were weighed individually (W1) and placed separately in 2% agar gel plates with the core facing the gel surface and incubated at 37°C ±1°C. At regular 1-hour time intervals until 8 hours, the tablet was removed from the Petri dish, and excess surface water was removed carefully with filter paper. The swollen tablet was then reweighed (W2) and the swelling index (SI) was calculated using the formula. The results listed in figure no 3.

% Swelling index = [(W 2 -W 1)/W 1] ×100

Bioadhesion Time [10]

The ex vivo mucoadhesion time was performed (n = 3) after application of the buccal tablet on freshly cut sheep buccal mucosa. The fresh sheep buccal mucosa was tied on the glass slide, and a mucoadhesive core side of each tablet was wetted with 1 drop of phosphate buffer pH 6.8 and pasted to the sheep buccal mucosa by applying a light force with a fingertip for 30 seconds. The glass slide was then put in the beaker, which was filled with 200 ml of the phosphate buffer pH 6.8, and was kept at 37°C ± 1°C. After 2 minutes, a 50-rpm stirring rate was applied to simulate the buccal cavity environment, and tablet adhesion was monitored for 16 hours. The time for the tablet to detach from the sheep buccal mucosa was recorded as the bioadhesion time. The results listed in figure no 4.

In-vitro dissolution studies of tablets [11]

Dissolution studies were carried out for all the formulations combinations in triplicate, employing USP XXVII paddle method and 900ml of pH 6.8 phosphate buffer as the dissolution medium. The medium was allowed to equilibrate to temp of 37°c ± 0.5°c. Tablet was placed in the vessel and the vessel was covered the apparatus was operated for 16 hrs in pH 6.8 phosphate buffer at 50 rpm. At definite time intervals of 5 ml of the aliquot of sample was withdrawn periodically and the volume replaced with equivalent amount of the fresh dissolution medium. The samples were analyzed spectrophotometrically at 353 nm using uv-spectrophotometer. The results listed in figure no 5.

Dissolution parameters

Apparatus	--	USP-II,
Dissolution Medium	--	pH 6.8 phosphate buffer
RPM	--	50
Sampling intervals	--	0,1,2,4,6,8,10,12,14,16.
Temperature	--	37°c ± 0.5°c

Infrared spectra analysis

Compatibility of the Drug with the excipients was determined by subjecting the physical mixture of the drug and the excipients of the main formulation to infrared absorption spectra analysis. Any changes in chemical composition of the drug after combining it with the excipients were investigated with I.R. spectral analysis. Infrared spectrum of Thiocolchicoside was determined on Fourier transform infrared spectrophotometer using KBr pellet method. The base line correction was done using dried Potassium bromide. Then the spectrum of the dried mixture of drug and Potassium bromide was done.

RESULTS AND DISCUSSION

Table 3: Evaluation data of buccoadhesive bilayer tablets

Form. Code	Avg. Weight (Mean±S.D) (n=20)	Hardness (Kg/cm2) (n=3)	Friability (n=20)	% Drug content (n=3)	Surface pH
F1	100.6±0.74	6±0.62	0.52	98.90±0.46	6.44±0.003
F2	101.7±0.62	7±0.57	0.29	99.84±0.72	6.53±0.025
F3	100.1±0.47	9±0.72	0.46	99.79±0.58	6.31±0.015
F4	101.2±0.23	8±0.58	0.36	98.44±0.62	6.46±0.005
F5	99.9±0.32	6±0.78	0.44	99.59±0.47	6.31±0.020
F6	99.1±0.54	8±0.48	0.59	100.34±0.53	6.64±0.087
F7	100.4±0.39	7±0.62	0.38	98.39±0.62	6.53±0.032
F8	102.1±0.32	6±0.46	0.46	100.89±0.54	6.66±0.012
F9	99.8±0.43	4±0.62	0.68	99.54±0.48	6.43±0.017

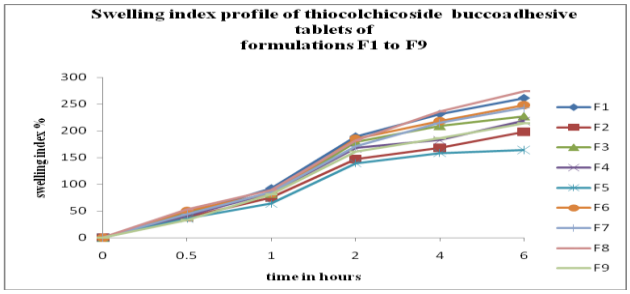

Figure 3: Swelling index profile of buccoadhesive bilayer tablets.

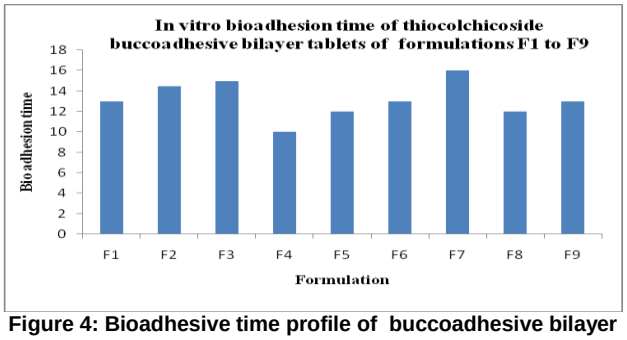

Figure 4: Bioadhesive time profile of buccoadhesive bilayer tablets.

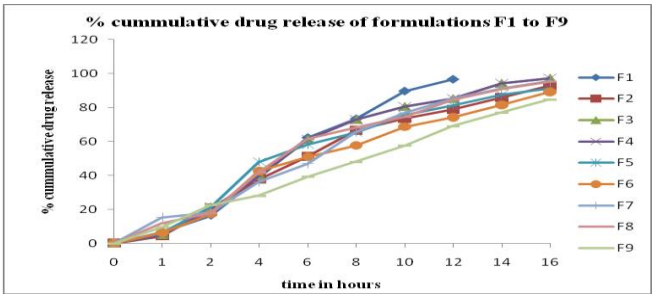

Figure 5: Dissolution data of buccoadhesive bilayer tablets.

IR spectroscopic studies for drug and drug-polymer interactions:

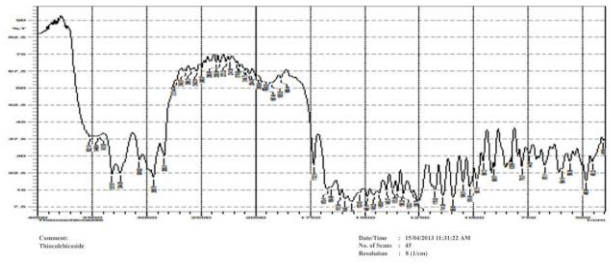

Figure 6: Spectra of pure drug of Thiocolchicoside

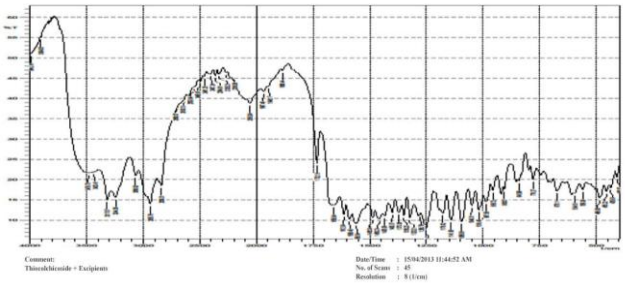

Figure 7: Spectra of Thiocolchicoside and excipients

IR Spectral analysis for drug alone and in combination with other excipients was carried out. There is no change in peaks of mixture when compared to pure drug, it indicates the absence of interaction.

CONCLUSION

In conclusion, the present study an attempt has been made to develop a novel buccoadhesive drug delivery system in the form of a tablet for the release of thiocolchicoside in unidirectional manner with improved bioavailability. Although all buccal tablets exhibited satisfying drug release, the best results were obtained with tablet of carbapol934P in combination with HPMC K4M (1:1).Invitro dissolution studies of the optimized formulation shows that the present drug release was 97.19% for 16 hrs for F3 formulation. These buccoadhesive formulations of buccoadhesive bilayer tablets were developed to a satisfactory level in terms of drug release, bioadhesive time, physicochemical properties and surface pH.

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